

# **Left ventricular diastolic dysfunction in atrial fibrillation**

## **Predictors and relation with symptom severity**

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## **Left ventricular diastolic dysfunction in atrial fibrillation**

### **Predictors and relation with symptom severity**

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Referat: Left ventricular diastolic dysfunction (LVDD) is common in the general population, but its prevalence in atrial fibrillation (AF), predictors for LVDD in AF and the association between LVDD and AF-related symptom severity has not been well-studied.

In 124 consecutive patients (mean age  $61 \pm 11$  years, 60 % male) with paroxysmal (n=70) or persistent AF (n=54) referred for AF catheter ablation, LVDD was evaluated according to current guidelines using transthoracic echocardiography. AF-related symptom severity was quantified using the EHRA score.

LVDD was present in 46 patients (37 %). In uni- and multivariable regression analysis, age (OR 1.068 per year, 95 % CI 1.023 – 1.115,  $p=.003$ ) and persistent AF (OR 2.427 vs paroxysmal AF, 95 % CI 1.112 – 5.3,  $p=.026$ ) were associated with LVDD. LVDD was found in 11 % with mild AF symptoms (n=27) as opposed to 44 % in patients with moderate- severe AF symptoms (n=97,  $p=.002$ ). Thus, the OR for moderate-severe AF symptoms was 6.368 (1.797 – 22.568,  $p=.004$ ) in the presence of LVDD.

LVDD (1) occurs frequently in AF, (2) is associated with advancing age and AF progression and (3) is correlated with symptom severity in AF.

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# **1 Introduction**

## **1.1 Left ventricular diastolic dysfunction**

### **1.1.1 Definition and pathophysiology**

The optimal performance of the left ventricle (LV) is dependent of ability to smoothly cycle between two states: a stiff, contracting chamber in which the pressure is rising rapidly leading to ejection of the stroke volume at arterial pressures (systole) and a compliant reservoir that allows the passive filling from low left atrial (LA) pressure (diastole).

The impairment of one of those components leads to deterioration of the whole system causing symptoms of heart failure.

In case of left ventricular diastolic dysfunction (LVDD) the distortion of the ventricle capacity to relax, stretch and passively fill at low pressure state during diastole results in development of chronic heart failure with normal left ventricular ejection fraction (HFNEF) (1).

Elevated filling pressures are the main physiologic consequence of diastolic dysfunction. There are considered elevated when the mean pulmonary capillary wedge pressure (PCWP) is >12 mm Hg or when the left ventricular end-diastolic pressure (LVEDP) is >16 mm Hg (1). Those pathological changes result in fatigue and breathlessness which are the first and most frequent symptoms of HFNEF. Through further aggravating of the underling LVDD the development of typical signs of heart failure such as lung crepitations, pulmonary edema, ankle swelling and hepatomegaly can be observed in advanced stages (1).

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The hemodynamic characteristics of LVDD can be caused by different factors and mechanisms. Besides external parameters such as the influence of the pericardium and the elevated pulmonary airway pressure, two processes can mainly affect pressure development in diastole.

At the beginning of the diastole the active relaxation of the myocardium and the recoil effect of elastic energy cumulated in the elastic fibers of extracellular matrix, which was stored in the myocardium during previous systole plays a key role. This ability of myocardium determines atrioventricular pressure gradient and ventricular filling rate. This relaxation of myocytes is an active adenosine triphosphate consuming process concerning the calcium homeostasis of cardiac myocytes. In patients with LVDD, the process of relaxation is slowed, resulting in a delay of mitral valve opening and a decrease in early diastolic atrioventricular pressure gradient. These effects lead to an impairment of early ventricular filling. This pathological hemodynamic may not be suffice to increase diastolic filling pressures at low heart rates, as there is still some reserve resulting from prolonged diastole, but at higher heart rates (e.g. in case of AF) it might elevated filling pressures to the level where symptoms of HFNEF can occur.

Apart from relaxation, the ventricular filling process is mainly influenced by the chamber stiffness, which represents the passive elastic capacity of the ventricle. This is dependent on cellular and histological structure of myocardium (cardiomyocytes and extracellular matrix), myocardial tone, chamber geometry, and wall thickness.

Those fundamental mechanisms of LVDD can be influenced by different comorbidities or conditions involving structural or histological remodeling (2) or even subcellular alterations (3). Therefore, certain systemic and cardiac diseases predispose to the development of LVDD with subsequent evolution of heart failure.

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Although diastolic dysfunction is not uncommon in patients with normal wall thickness, LV hypertrophy is among the most important reasons for development of LVDD (4). In patients with HFNEF, concentric hypertrophy (increased mass and relative wall thickness), or remodeling (normal mass but increased relative wall thickness), can be frequently observed. Because of the high prevalence of hypertension, especially in the older population, LV hypertrophy is common, and hypertensive heart disease is the most common abnormality leading to diastolic heart failure (4).

Diabetic cardiomyopathy is characterized by altered myocardial and vascular function in the absence of macroscopic coronary artery disease, hypertension, and valvular or congenital heart disease (5). These patients exhibit changes in cardiac structure such as ventricular and myocyte hypertrophy, perivascular fibrosis, increased deposition of matrix collagen which were observed in different studies (6,7). Furthermore, in diabetic patients a different composition of myocardial cell membrane lipids, cellular triglycerides may be observed (8). The microvascular changes e.g. endothelial dysfunction and the mediated fibrosis increases arterial stiffness (7). In those patients the diastolic abnormalities are usually the first cardiac pump dysfunctions that can be detected (9).

Since a ventricular diastolic relaxation is an energy-dependent process, it may be impaired by conditions decreasing energy availability such as ischemia (10). Therefore, in a series of studies a high prevalence of LVDD was associated with coronary artery disease (11,12).

### **1.1.2 Echocardiographic diagnostic methods**

The identification of the elevated filling pressure had been initially based on an interventional

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measurements during catheterisation. However, with the development of modern echocardiographic techniques enabling non-invasive assessment of diastolic function, echocardiography has gained a central role in the evaluation of LVDD over the past two decades. Today two echocardiographic measurements are widely acknowledged and recommended by the guidelines (13) for the diagnosis of LVDD: 1) mitral inflow pattern obtained by the use of pulse wave Doppler and 2) the mitral annular velocities.

Primary measurements of mitral inflow include the peak early filling (E-wave) and late diastolic filling (A-wave) velocities, the E/A ratio, deceleration time (DT) of early filling velocity (Figure 1). The values of mitral E/A ratio and DT identify different mitral inflow patterns which are specific for three stages of LVDD. They include impaired LV relaxation pattern, pseudonormal LV filling (PNF) and restrictive LV filling.

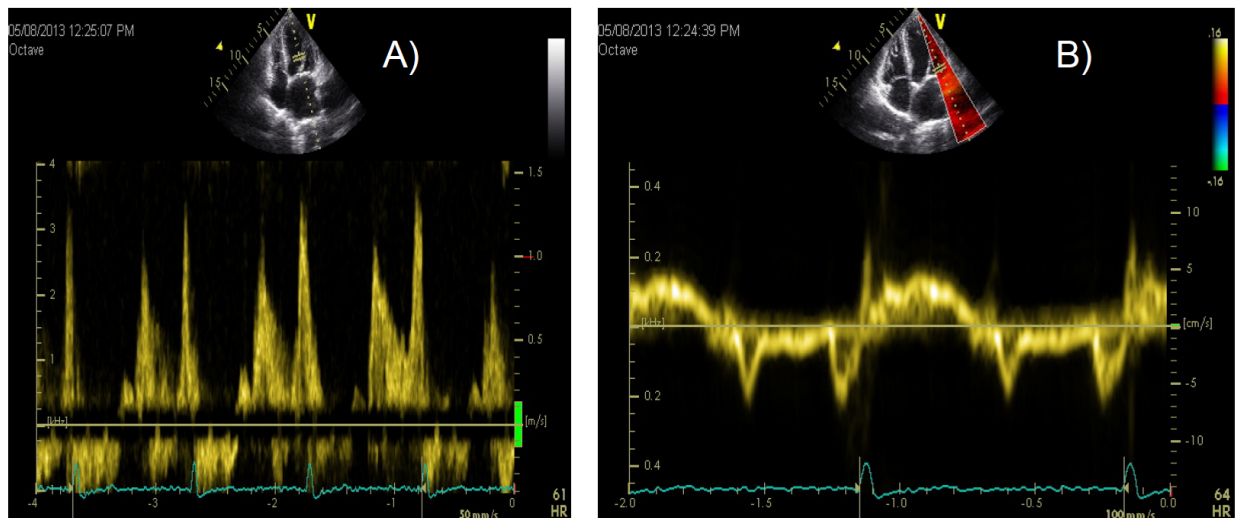


Figure 1. A) mitral inflow pattern obtained by the use of pulse wave Doppler and B) the mitral annular velocities depicted by tissue Doppler.

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However, this method has serious limitation reducing its diagnostic value as the LV filling patterns have a U-shaped relation with LV diastolic function, meaning that similar values can be seen in healthy normal subjects and patients with LVDD. Therefore, the diagnosis should not be based on mitral inflow pattern alone but be combined with the tissue Doppler measurements.

The mitral annular velocities measured by tissue Doppler, so called  $e'$ , is a more sensitive parameter for abnormal myocardial early diastolic function than mitral variables and can be used to draw inferences about LV relaxation process. Once mitral flow, annular velocities are acquired, it is possible to compute additional ratio. The ratio include inflow E velocity to tissue Doppler  $e'$  ( $E/e'$  ratio)(14), which plays an important role in the estimation of LV filling pressures. This so-called filling index, correlates well with LV filling pressure and allows for diagnosis of diastolic dysfunction if it reaches high values.

Based on this comprehensive echocardiographic measurements, the current guidelines (13) recommend grading of LVDD in mild or grade I (impaired relaxation pattern), moderate or grade II (PNF), and severe (restrictive filling) or grade III (Figure 2). In patients with mild diastolic dysfunction, the mitral E/A ratio is  $< 0.8$ , DT is  $>200$  ms, and the  $E/e'$  ratio is  $<8$ . In patients with moderate diastolic dysfunction (grade II), the mitral E/A ratio is 0.8 to 1.5 (pseudonormal) and decreases by 50% during the Valsalva maneuver, the  $E/e'$  (average) ratio is 9 to 12, and  $e'$  is  $<8$  cm/s. Grade II diastolic dysfunction represents impaired myocardial relaxation with mild to moderate elevation of LV filling pressures. With severe diastolic dysfunction (grade III), restrictive LV filling occurs with an E/A ratio  $> 2$ , DT  $<160$  ms and average  $E/e'$  ratio  $>13$ .



Grade I impaired relaxation	Grade II pseudonormal filling	Grade III restrictive filling
$E/A < 0.8$ $DT > 200\text{ms}$ $E/e' < 8$	$E/A \ 0.8\text{-}1.5$ $DT \ 160\text{-}200\text{ms}$ $E/e' \ 9\text{-}12$	$E/A > 2$ $DT < 160\text{ms}$ $E/e' > 13$

Figure 2. Grading of LVDD

### 1.1.3 Increasing prevalence and importance of left ventricular diastolic dysfunction

About half of patients with new diagnoses of heart failure have normal or near normal global ejection fractions (15-21). Although the term diastolic heart failure has been abandoned, LVDD is considered to be the main pathophysiologic mechanisms in those patients.

The average age of those patients tends to be older than those with reduce EF and in most studies the majority have been women and have a history of hypertension (15-16). Therefore, the aging of the populations combined with increasing prevalence of hypertension, which is often poorly treated, indicate a substantial increase in the number of patients with HFNEF in foreseeable future (22).

Although, in comparison to heart failure secondary to reduce of EF the HFNEF rarely have fulminate course and the signs and symptoms remain subclinical for long time, the outcome might be similar.

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Epidemiological studies have shown that the annual mortality rate approaches 15% for patients with HFNEF, which is a similar rate as in patients with reduce EF (15,20,23). Importantly, even in asymptomatic patients with grade I LVDD, diastolic dysfunction was associated with a 5-fold higher 3-year to 5-year mortality in comparison with subjects with normal diastolic function (24).

This issue is of great importance as till today no evidence based therapy have been established. Since previously patients with HFNEF have been excluded from clinical trials on the basis of a normal LV ejection fraction there is little evidence to guide treatment. Nevertheless, multiple drugs which are used for therapy of systolic heart failure, including beta-blockers, sartans, diuretics and cardiac glycosides, were tested in large trials (24-30). Most of the agents had a modest impact in preventing hospital admissions and improving symptoms and signs of HFNEF but non had an significant effect on cardiovascular death.

## **1.2 Link between left ventricular diastolic dysfunction and atrial fibrillation**

The interactions between AF and LVDD are frequently of bidirectional nature and can be explained on haemodynamical, structural or even cellular level.

For instance, patients with abnormal diastolic function are frequently hospitalised due to signs of heart failure (23) and the odd ratio increases in presence of AF (31). An possible explanation of that observation would be a strong dependence of the hemodynamic performance of the whole system on intact atrial function since the functional reserve of impaired ventricle is highly reduced. Consequently, the rapid deterioration associated with onset of AF might be leading to

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increased hospitalisation or even influence outcome (32,33).

The presence of LVDD has been also proven to be correlated with higher thromboembolic risk in AF patients (34). Increased ventricular ‘stiffness’ and poor myocardial compliance, which are associated with LVDD, may cause abnormal blood flow characteristics, which may promote thrombogenesis. In addition, worse atrial function and stasis, which can be secondary to elevated LV filling pressures, may boost prothrombotic processes. LVDD may also influence the cellular balance of the whole cardiovascular system. Preliminary study showed a significant correlation between diastolic dysfunction and functional impairment of endothelial cells, suggesting increased thrombogenic potential (35). Furthermore, LVDD may be associated with increased prothrombotic tendency at the molecular level. It has been described that higher intravascular fibrin turnover, reflected by plasma D-dimer concentration, can be observed in patients with LVDD, when compared to a normal population (36).

The increasing availability and improved techniques of invasive electrophysiology revealed further interactions between LVDD and AF as it has been shown that patients with LVDD have more severe LA low-voltage substrate, when compared to the patients with normal cardiac function (37). Since LA diameter and volume increase with an increasing severity of the diastolic dysfunction it can also result in a chronic diastolic atrial pressure overload, and subsequent LA remodeling.

Consequently, recent reports suggested that hemodynamical alterations associated with impaired diastolic function can influence the results of catheter ablation (38-40). One possible mechanism of AF induction and therapy failure in LVDD patients is a progressive atrial remodeling associated with an enlarged left atrium (41,42) and higher wall stress resulting from increased

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LA pressure (43). Those processes may create a low-voltage substrate and induce focal automaticity, subsequently promote AF and worsen interventional outcomes.

## **2 Aim of the study**

The aim of the study was to define prevalence and predictors for LVDD in AF and to examine the potential association between LVDD and AF-related symptom severity

## **3 Publication**

Kosiuk J, Van Belle Y, Bode K, Kornej J, Arya A, Rolf S, Husser D, Hindricks G, Bollmann A. Left ventricular diastolic dysfunction in atrial fibrillation: predictors and relation with symptom severity. J Cardiovasc Electrophysiol. 2012 Oct;23(10):1073-1082

## Left Ventricular Diastolic Dysfunction in Atrial Fibrillation: Predictors and Relation with Symptom Severity

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**Left Ventricular Diastolic Dysfunction in Atrial Fibrillation. Background:** Left ventricular diastolic dysfunction (LVDD) is common in the general population, but its prevalence in atrial fibrillation (AF), predictors for LVDD in AF and the association between LVDD and AF-related symptom severity has not been well studied.

**Methods:** In 124 consecutive patients (mean age  $61 \pm 11$  years, 60% male) with paroxysmal ( $n = 70$ ) or persistent AF ( $n = 54$ ) referred for AF catheter ablation, LVDD was evaluated according to current guidelines using transthoracic echocardiography. AF-related symptom severity was quantified using the European Heart Rhythm Association score.

**Results:** LVDD was present in 46 patients (37%). In uni- and multivariable regression analysis, age (OR 1.068 per year, 95% CI 1.023–1.115,  $P = 0.003$ ) and persistent AF (OR 2.427 vs. paroxysmal AF, 95% CI 1.112–5.3,  $P = 0.026$ ) were associated with LVDD. LVDD was found in 11% with mild AF symptoms ( $n = 27$ ) as opposed to 44% in patients with moderate–severe AF symptoms ( $n = 97$ ,  $P = 0.002$ ). Thus, the OR for moderate–severe AF symptoms was 6.368 (1.797–22.568,  $P = 0.004$ ) in the presence of LVDD.

**Conclusions:** LVDD (1) occurs frequently in AF, (2) is associated with advancing age and AF progression and (3) is correlated with symptom severity in AF. (*J Cardiovasc Electrophysiol*, Vol. 23, pp. 1073–1077, October 2012)

*atrial fibrillation, catheter ablation, diastolic dysfunction, echocardiography, heart failure*

### Introduction

Several studies suggest that almost half of the patients with heart failure symptoms have left ventricular diastolic dysfunction (LVDD). The proportion of patients with LVDD in the various heart failure cohorts ranges from 13% to 74% (with a mean of 40%).<sup>1</sup> Population-based epidemiologic studies report a high prevalence (25–30%) of atrial fibrillation (AF) among patients with LVDD.<sup>2</sup> Conversely, it was also shown that diastolic dysfunction is a predictor of future AF.<sup>3</sup> Moreover, AF increased the risk of death and thromboembolic complications in patients with LVDD.<sup>4,5</sup>

Predictors of LVDD have been identified and include diabetes or hypertension, but analysis has been restricted to the general population or patients in sinus rhythm.<sup>2</sup>

In advanced stages, LVDD causes typical signs and symptoms of heart failure such as lung crepitations, pulmonary edema, dependent edema, hepatomegaly, dyspnea on exertion and fatigue.

Similarly, AF can cause heart failure symptoms either through a tachycardiomyopathy or by exacerbating an underlying heart failure condition. However, there is lack of data about the relation between LVDD and AF symptoms.

Consequently, this study explored the prevalence and predictors of LVDD, and the association between LVDD and AF-related symptom severity in 124 patients with paroxysmal or persistent AF referred for AF catheter ablation and assessed its possible influence on rhythm outcome after ablation.

### Methods

#### Patients

Of 240 consecutive patients with paroxysmal or persistent AF included prospectively in our institutional AF catheter ablation registry, 83 were excluded because of prior catheter ablation, 21 had an implanted pacemaker or defibrillator, and 12 had mitral valve disease or prosthesis. Consequently, the final study population comprises 124 patients (Table 1).

Paroxysmal and persistent AF were defined according to current guidelines.<sup>6</sup> Paroxysmal AF was defined as self-terminating within 7 days after onset. Persistent AF was defined as an AF episode either lasting longer than 7 days or requiring drug or direct current cardioversion for termination. Patients with persistent AF underwent direct current cardioversion at least 14 days prior to echocardiography. AF-related symptom severity was quantified using the European Heart Rhythm Association (EHRA) score;<sup>7</sup> i.e., EHRA I as “no symptoms,” EHRA II as “mild symptoms” that do not

Parts of this study were presented at the Europace 2011 Congress and the ESC Congress 2011.

No disclosures.

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TABLE 1  
Baseline, Clinical, and Echocardiographic Data of the Study Population  
(n = 124)

Age (years)	61 ± 10
Males/females, n (%)	74/50 (60/40)
BMI (kg/m <sup>2</sup> )	29 ± 5
Diabetes mellitus, n (%)	21 (17)
CAD, n (%)	16 (13)
Hypertension, n (%)	97 (78)
Paroxysmal AF/persistent AF, n (%)	70/54 (56/44)
CHADS2 score, n (%)	
0	18 (15)
1	49 (40)
2	39 (31)
3	13 (10)
4	5 (4)
EHRA score, n (%)	
1	0 (0)
2	27 (22)
3	91 (73)
4	6 (5)
NYHA class, n (%)	
1	88 (71)
2	30 (24)
3	6 (5)
4	0 (0)
Beta blockers, n (%)	103 (83)
ACEIs/ARBs, n (%)	75 (60)
Calcium channel blockers, n (%)	6 (5)
Antiarrhythmic drugs, n (%)	59 (48)
Cardiac glycoside, n (%)	11 (9)
Diuretics, n (%)	27 (22)
LVEF (%)	62 ± 8
LAD (mm)	41 ± 6
IVSd (mm)	12 ± 2
E (m/s)	0.8 ± 0.2
A (m/s)	0.6 ± 0.2
E/A	1.6 ± 0.9
E/E'	8 ± 3
Stage of LVDD, n (%)	
0	78 (63)
1	26 (21)
2	16 (13)
3	4 (3)

A = atrial filling velocity; ACEI = angiotensin converting enzyme inhibitors; AF = atrial fibrillation; ARB = angiotensin II receptor antagonists; CAD = coronary artery disease; E = mitral early diastolic peak velocity; LAD = left atrial diameter; LVDD = left ventricular diastolic dysfunction; LVEF = left ventricular ejection fraction; IVSd = interventricular septal end diastolic dimension.

affect daily activity, EHRA III as "severe symptoms" that affect daily activity and EHRA IV as disabling symptoms discontinuing normal daily activity.

The study was approved by the local ethics committee and patients provided written informed consent for participation.

#### Echocardiography

All patients underwent comprehensive Doppler and M-mode transthoracic echocardiography during sinus rhythm before the catheter ablation according to the recommendations of the American Society of Echocardiography.<sup>3</sup> The Vivid-7 System and Vivid-9 System (Vingmed-General Electric, Milwaukee, WI, USA) with a 3.6-MHz probe were used for echocardiography. The LA dimension was measured in the parasternal long axis view at end systole. The left ventricular ejection fraction (LVEF) was assessed by monoplane Simpson's method.

Mitral diastolic inflow was interrogated using pulsed-wave Doppler from the apical 4-chamber view with the sample volume placed at the level of the mitral leaflet tips. Mitral early diastolic peak (E-wave) and late peak (A-wave) velocities, E/A ratio, and deceleration time (DT) of mitral early velocity were measured. An apical 4-chamber view was also used to obtain Doppler tissue imaging of the lateral mitral annulus. Early diastolic mitral annulus peak velocity was measured, and the ratio of transmitral diastolic peak velocity to the mitral annular diastolic peak velocity (E/e') was calculated.

LVDD was graded according to current recommendations<sup>9</sup> as grade 1: the mitral E/A < or = 0.8, DT > 200 milliseconds, and E/e' < or = 8; grade 2: 0.8 < E/A < 1.5, 160 milliseconds < DT < 200 milliseconds, and 9 < E/e' < 12; or grade 3: E/A > or = 2, DT < 160 milliseconds, and E/e' > 12.

#### Catheter Ablation and Follow-Up

Left atrial catheter ablation was performed using a previously described approach.<sup>10,11</sup> In all patients circumferential left atrial ablation lines were placed around the antrum of the ipsilateral pulmonary veins (irrigated tip catheter, preselected tip temperature of 48 °C, and maximum power of 30–50 W). In patients with persistent AF, additional linear lesions were added at the left atrial roof, the basal posterior wall and the left atrial isthmus. Ablation of complex fractionated electrograms was not performed. The isolation of all pulmonary veins with bidirectional block was verified with a multipolar circular mapping catheter and was defined as the procedural endpoint.

In all patients 7-day Holter recordings were performed immediately after the ablation, and during 6 and 12 months follow-up. Early AF recurrence was defined as a documented AF episode lasting longer than 30 seconds during the first week after the ablation, which is in alignment with previous definitions.<sup>11</sup> Late recurrence of AF between 4 and 12 months follow-up (thus including a 3-month blanking period) was defined as any documented AF episode (including 7-day Holter at 6 and 12 months after the ablation).

#### Statistical Analysis

Continuous variables are reported as mean ± 1 standard deviation and categorical variables are reported as frequencies. Continuous variables were compared using the Student *t*-test and categorical variables were compared using the chi-square test.

Multivariable regression analysis that included variables with a P value < 0.1 found in univariate analysis was performed to identify independent predictors of LVDD and symptom severity.

A P value of < 0.05 was considered statistically significant.

#### Results

##### Predictors of LVDD in AF Patients

LVDD was present in 46 patients (37%), showing grade I in 26 (21%), grade II in 16 (13%), and grade III in 4 (3%) patients. In univariate analysis, older age, the presence of coronary artery disease (CAD), and persistent AF



## - Discussion -

TABLE 2

Clinical and Echocardiographic Variables in Patients with and without LVDD

	Left Ventricular Dysfunction Diastolic		P Value
	No (n = 78)	Yes (n = 46)	
Age (years)	59 ± 11	65 ± 9	0.002
Males, n (%)	45 (58)	29 (63)	0.557
BMI (kg/m <sup>2</sup> )	29 ± 6	29 ± 5	0.705
Diabetes mellitus, n (%)	10 (13)	11 (24)	0.112
Hypertension, n (%)	59 (76)	38 (83)	0.364
CAD, n (%)	6 (8)	10 (22)	0.024
Persistent AF, n (%)	28 (36)	26 (57)	0.025
CHADS2 score, n (%)			0.005
0	14 (18)	4 (9)	
1	35 (45)	14 (30)	
2	24 (31)	15 (33)	
3	5 (6)	8 (17)	
4	0 (0)	5 (11)	
EHRA score, n (%)			0.006
1	0 (0)	0 (0)	
2	24 (31)	3 (7)	
3	50 (64)	41 (89)	
4	4 (5)	2 (4)	
NYHA class, n (%)			0.324
1	59 (76)	29 (63)	
2	16 (21)	14 (30)	
3	3 (3)	3 (7)	
4	0 (0)	0 (0)	
Beta blockers, n (%)	64 (82)	39 (85)	0.695
ACEIs/ARBs, n (%)	45 (58)	30 (65)	0.408
Calcium channel blockers, n (%)	3 (4)	3 (7)	0.502
Antiarrhythmic drugs, n (%)	35 (45)	24 (53)	0.366
Cardiac glycoside, n (%)	7 (9)	4 (9)	0.958
Diuretics, n (%)	15 (19)	12 (26)	0.372
LVEF (%)	62 ± 8	61 ± 6	0.348
LAD (mm)	41 ± 6	42 ± 6	0.364
IVSd (mm)	11 ± 2	12 ± 2	0.088
E (m/s)	0.8 ± 0.2	0.7 ± 0.2	0.090
A (m/s)	0.5 ± 0.1	0.7 ± 0.2	<0.001
E/A	1.9 ± 0.9	1.2 ± 0.6	<0.001
E/E'	6.7 ± 1.8	10 ± 4	<0.001

Abbreviations as in Table 1.

were associated with LVDD, while other clinical or echocardiographic variables were not (Table 2).

Using multivariable regression analysis, age (OR 1.068 per year, 95% CI 1.023–1.115,  $P = 0.003$ ) and persistent AF (OR 2.427 vs paroxysmal AF, 95% CI 1.112–5.3,  $P = 0.026$ ) were independent predictors of LVDD.

### LVDD and AF Symptom Severity

Mild symptoms (EHRA score II) were present in 27 patients (22%), while the remaining 97 patients (78%) suffered from moderate to severe symptoms (EHRA score III and IV, Table 1). Patients with mild symptoms were comparable in their clinical characteristics to patients with moderate/severe symptoms (Table 3). However, LVDD was found in 11% with mild as opposed to 44% in patients with moderate–severe AF symptoms ( $P = 0.002$ ) (Table 4). Thus, the OR for moderate–severe AF symptoms was 6.368 (1.797–22.568,  $P = 0.004$ ) in the presence of LVDD.

### LVDD and Rhythm Outcome of Catheter Ablation

Complete pulmonary vein isolation as procedural endpoint was achieved in all patients. All patients completed the

TABLE 3

Clinical and Echocardiographic Variables in Patients with and without Moderate–Severe AF Symptoms

	Moderate–Severe AF Symptoms		P Value
	No (n = 27)	Yes (n = 97)	
Age (years)	60 ± 9	62 ± 11	0.433
Males, n (%)	15 (56)	59 (61)	0.622
BMI (kg/m <sup>2</sup> )	30 ± 7	28 ± 5	0.088
Diabetes mellitus, n (%)	4 (15)	17 (18)	0.740
CAD, n (%)	1 (4)	15 (16)	0.107
Hypertension, n (%)	20 (74)	77 (79)	0.555
Persistent AF, n (%)	10 (37)	44 (45)	0.440
CHADS2 score, n (%)			0.708
0	5 (18)	13 (14)	
1	12 (44)	37 (38)	
2	8 (30)	31 (32)	
3	1 (4)	12 (12)	
4	1 (4)	4 (4)	
NYHA class, n (%)			0.934
1	19 (70)	69 (71)	
2	7 (26)	23 (24)	
3	1 (4)	5 (5)	
4	0 (0)	0 (0)	
Beta blockers, n (%)	23 (85)	80 (83)	0.740
ACEIs/ARBs, n (%)	17 (63)	58 (60)	0.766
Calcium channel blockers, n (%)	1 (4)	5 (5)	0.756
Antiarrhythmic drugs, n (%)	12 (44)	47 (49)	0.678
Cardiac glycosides, n (%)	2 (7)	9 (9)	0.762
Diuretics, n (%)	5 (19%)	22 (23%)	0.643
LVEF (%)	61 ± 7	67 ± 7	0.421
LAD (mm)	42 ± 5	41 ± 6	0.490
IVSd (mm)	12 ± 5	12 ± 6	0.499
LVDD (%)	11	44	0.002
E (m/s)	0.8 ± 0.2	0.8 ± 0.2	0.414
A (m/s)	0.5 ± 0.2	0.6 ± 0.2	0.334
E/A	1.6 ± 0.8	1.6 ± 0.9	0.934
E/E'	6.4 ± 1.4	8.4 ± 3.5	0.021

Abbreviations as in Table 1.

TABLE 4

LVDD and AF Symptom Severity

	Left Ventricular Diastolic Dysfunction			
	No, n (%)	1, n (%)	2, n (%)	3, n (%)
EHRA I	0 (0)	0 (0)	0 (0)	0 (0)
EHRA II	24 (19)	3 (2)	0 (0)	0 (0)
EHRA III	50 (40)	22 (18)	15 (12)	4 (3)
EHRA IV	4 (3)	1 (1)	1 (1)	0 (0)

short-term follow-up including 7-day Holter electrocardiograms (ECGs). Early AF recurrence occurred in 42 patients (34%). The long-term follow-up, including 7-day Holter ECGs, was completed by 115 patients (93%) at 6 months and by 93 patients (75%) after 12 months. Late AF recurrence was observed in 26 patients (27%). The presence or stage of LVDD was not related with early and late recurrence.

## Discussion

### Main Findings

In this study LVDD predictors and its relations to symptoms were investigated in 124 patients with AF. We observed a high prevalence of LVDD among symptomatic AF patients.



LVDD was correlated with age, persistent AF and its presence was associated with more severe AF symptoms.

#### LVDD in AF

The prevalence of LVDD was relatively high (37%) in our population of symptomatic AF patients with mostly sub-clinical heart failure symptoms (71% in New York Heart Association [NYHA] I, 24% in NYHA II, 5% NYHA III, no patients with NYHA IV). In previous trials describing the population of patients admitted due to heart failure, the LVDD was observed in up to 30% of cases.<sup>2</sup>

Since a ventricular diastolic relaxation is an energy-dependent process, it may be impaired by conditions decreasing energy availability such as ischemia.<sup>12</sup> In fact, as shown in univariate analysis, CAD was more common in patients with impaired diastolic function (7% vs 22%,  $P=0.024$ ). In our cohort, LVDD was also significantly correlated with advanced age (OR 1.068 per year, 95% CI 1.023–1.115,  $P=0.003$ ) as the reduced ventricular compliance is secondary to the ageing process, since the ventricular stiffness increases with age and impairs diastolic function altering LV filling pressures.<sup>13</sup>

The interaction between this type of heart failure and AF is further confounded by evidence that diastolic dysfunction is itself a predictor of future AF.<sup>3</sup>

AF impairs cardiac function by several mechanisms, such as the loss of atrioventricular synchrony and atrial contraction, the reduction of the diastolic filling, and the induction of a tachycardia-induced cardiomyopathy. It therefore can be expected that the restoration of sinus rhythm will positively influence the ventricular function. Recent publications<sup>14–16</sup> support that hypothesis demonstrating effectiveness of catheter ablation and proving existence of additional benefits of this interventional approach.

Cha *et al.*<sup>14</sup> described an improvement of LVDD of at least 1 grade in 30% of patients undergoing AF catheter ablation. Similar results were published by Reant *et al.*<sup>15</sup> who performed an echocardiographic study of LV diastolic and systolic function in a group of patients with paroxysmal and chronic AF who underwent catheter ablation, demonstrating that systolic and diastolic function of the left chamber improved after AF ablation. Studies on patients undergoing the surgical radiofrequency ablation also demonstrated reverse remodeling of left ventricular diastolic and systolic function.<sup>16</sup>

The authors hypothesized that LV diastolic dysfunction can be attributed at least in part to AF. The suspected pathophysiological mechanisms were accounted to AF-induced stretch of the LA and the pulmonary veins. However, another potentially important reason for diastolic dysfunction is AF-induced alterations in the Ca<sup>2+</sup> regulatory proteins that are responsible for both electrical and mechanical myocyte function.

Our results mirrored the preliminary findings of other groups, which showed an improvement of LVDD by cessation of AF or reducing the AF burden. Accordingly, we have observed an increased frequency and more severe LVDD in patients with a persistent form of AF. This raises the question of whether AF contributes to development of diastolic failure, rather than to be a secondary problem.

Patients with abnormal diastolic function are frequently hospitalized due to signs of heart failure<sup>1,17</sup> and the odd ratio

increases in the presence of AF,<sup>18</sup> but little is known about AF symptoms in those groups of patients. Moreover, little is known about determinants of symptoms or symptom severity in AF. Valvular heart disease and diuretics treatment are more likely to occur among symptomatic patients,<sup>19</sup> but no relationship between the presence of LVDD and the severity of AF symptoms was reported. Since valvular heart disease can cause alterations in LV filling pattern and diuretics are generally used to treat symptoms of heart failure with normal ejection fraction, both conditions can be linked to LVDD. Consequently, LVDD may be seen as pathway explaining our results showing that patients with LVDD have more severe symptoms related to AF. A possible explanation of that observation would be a strong dependence of the hemodynamic performance of the whole system on intact atrial function since the functional reserve of the impaired left ventricle is highly reduced. With the increasing use of AF catheter ablation and an increasing prevalence of LVDD, the possible association between LVDD and procedural outcome deserves further investigation. In contrast to recent reports,<sup>20</sup> we have not observed any relationship between LVDD and early or late AF recurrence.

#### Limitations

This study included a highly selected patient population, i.e., patients referred for catheter ablation had drug-refractory AF in most cases. None of the patients was asymptomatic. Consequently, it is not known whether the described predictors can be found in the general AF population. Because of echocardiographic limitations only patients presenting with sinus rhythm were enrolled in this study. No information regarding the quality of rate control during AF was available, which prohibits analyzing the effects of ventricular rate during AF on both LVDD and symptom severity. Although we have not found an association between LVDD and AF recurrence, a detailed analysis of echocardiographic parameters is still ongoing including a longer follow-up period and LVDD changes after ablation.

#### Conclusions

LVDD (1) occurs frequently in AF, (2) is associated with advancing age and persistent AF, and (3) is correlated with symptom severity in AF.

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## 4 Discussion

The prevalence of LVDD was relatively high (37%) in our population of symptomatic AF patients with mostly subclinical heart failure symptoms (71% in NYHA I, 24% in NYHA II, 5% NYHA III, no patients with NYHA IV). In previous trials describing the population of patients admitted due to heart failure, the LVDD was observed in up to 30% of cases (4).

Since a ventricular diastolic relaxation is an energy-dependent process, it may be impaired by conditions decreasing energy availability such as ischemia (10). In fact, as shown in univariate analysis, CAD was more common in patients with impaired diastolic function (7% vs 22%,  $p=0.024$ ). In our cohort, LVDD was also significantly correlated with advanced age (OR 1.068 per year, 95 % CI 1.023 – 1.115,  $p=.003$ ) as the reduced ventricular compliance is secondary to ageing process, since the ventricular stiffness increases with age and impairs diastolic function altering LV filling pressures (43).

The interaction between this type of heart failure and AF is further confounded by evidence that diastolic dysfunction is itself a predictor of future AF (44).

AF impairs cardiac function by several mechanisms, such as the loss of atrio-ventricular synchrony and atrial contraction, the reduction of the diastolic filling, the induction of a tachycardia-induced cardiomyopathy. It can be therefore expected that the restoration of sinus rhythm will positively influence the ventricular function. Recent publications (39, 45) support that hypothesis demonstrating effectiveness of catheter ablation and proving existence of additional benefits of this interventional approach.

Cha et al. (39) described an improvement of LVDD of at least 1 grade in 30% of patients

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undergoing AF catheter ablation. Similar results were published by Reant et al. (45) who performed an echocardiographic study of LV diastolic and systolic function in a group of patients with paroxysmal and chronic AF who underwent catheter ablation, demonstrating that systolic and diastolic function of the left chamber improved after AF ablation. Studies on patient ongoing the surgical radiofrequency ablation also demonstrated reverse remodelling of left ventricular diastolic and systolic function (46).

The authors hypothesized that LV diastolic dysfunction can be attributed at least in part to AF. The suspected pathophysiological mechanisms were accounted to AF-induced stretch of the LA and the pulmonary veins. However, another potentially important reason for diastolic dysfunction is AF-induced alterations in the  $Ca^{2+}$  regulatory proteins that are responsible for both electrical and mechanical myocyte function.

Our results mirrored the preliminary findings of other groups which showed an improvement of LVDD by cessation of AF or reducing the AF burden. Accordingly we observed an increased frequency and more severe LVDD in patients with a persistent form of AF. This raises the question of whether AF contributes to development of diastolic failure, rather than to be a secondary problem.

Patients with abnormal diastolic function are frequently hospitalised due to signs of heart failure (23) and the odd ratio increases in presence of AF (31) but little is known about AF symptoms in those group of patients. Moreover, little is known about determinants of symptoms or symptom severity in AF. The valvular heart disease as well as diuretics treatment are more likely to occur amongst symptomatic patients (47) but no relationships between presence of LVDD and the severity of the AF symptoms were reported. Since valvular heart disease can cause alterations in

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LV filling pattern and diuretics are generally used to treat symptoms of heart failure with normal ejection fraction both conditions can be linked to LVDD. Consequently, LVDD may be seen as a pathway explaining our results showing that patients with LVDD have more severe symptoms related to AF. A possible explanation of that observation would be a strong dependence of the hemodynamic performance of the whole system on intact atrial function since the functional reserve of the impaired ventricle is highly reduced.

## **5 Limitations**

This study included a highly-selected patient population, i.e. patients referred for catheter ablation had drug-refractory AF in most cases. None of the patients was asymptomatic. Consequently, it is not known whether the described predictors can be found in the general AF population. Due to echocardiographic limitations only patients presenting with sinus rhythm were enrolled in this study.

## **6 Conclusion**

The left ventricular diastolic dysfunction occurs frequently in patients with atrial fibrillation and is associated with advancing age and persistent type of atrial fibrillation. Furthermore, left ventricular diastolic dysfunction is associated with a higher symptom severity in atrial fibrillation.

- *Discussion* -



## 7 Synopsis

Dissertation zur Erlangung des akademischen Grades Dr. med.

### **Left ventricular diastolic dysfunction in atrial fibrillation**

#### **Predictors and relation with symptom severity**

Eingereicht von: Dr.med.univ. Jędrzej Kosiuk

Angefertigt am: Herzzentrum der Universität Leipzig

Betreut von: Prof. Dr. med. A. Bollmann

August 2013

Left ventricular diastolic dysfunction (LVDD) is common in the general population, but its prevalence in atrial fibrillation (AF), predictors for LVDD in AF and the association between LVDD and AF-related symptom severity has not been well-studied.

In 124 consecutive patients (mean age  $61 \pm 11$  years, 60 % male) with paroxysmal (n=70) or persistent AF (n=54) referred for AF catheter ablation, LVDD was evaluated according to current guidelines using transthoracic echocardiography. AF-related symptom severity was quantified using the EHRA score.

LVDD was present in 46 patients (37 %). In uni- and multivariable regression analysis, age (OR 1.068 per year, 95 % CI 1.023 – 1.115,  $p=.003$ ) and persistent AF (OR 2.427 vs paroxysmal AF, 95 % CI 1.112 – 5.3,  $p=.026$ ) were associated with LVDD. LVDD was found in 11 % with mild AF symptoms (n=27) as opposed to 44 % in patients with moderate- severe AF symptoms (n=97,  $p=.002$ ). Thus, the OR for moderate-severe AF symptoms was 6.368 (1.797 – 22.568,  $p=.004$ ) in the presence of LVDD.

LVDD (1) occurs frequently in AF, (2) is associated with advancing age and AF progression and (3) is correlated with symptom severity in AF.

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## 9 Erklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren.

.....

Datum

.....

Unterschrift



## 10 Curriculum vitae

### ***Persönliche Daten***

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*Geburtsdatum*

20. März 1981

*Geburtsort*

Wroclaw (Breslau), Polen

*Staatsangehörigkeit*

Polen

*Familienstand*

verheiratet, ein Sohn

### ***Ausbildung***

---

**2002 – 2007** Studium der Humanmedizin, Medizinische Universität Wien

*Promotion am 20. September 2007 zum Dr. med. univ.*

**2000 – 2002** Medizinstudium an der Schlesischen Akademie für Medizin in Katowice

### ***Berufliche Tätigkeiten***

---

**2008 – dato** Assistenzarzt in der Abteilung für Rhythmologie, Herzzentrum Leipzig

**2007 – 2008** Wissenschaftliche Mitarbeit an der Universitätsklinik für Notfallmedizin am einen Projekt zur experimentellen Reanimationsforschung, Medizinische Universität Wien

**2005 – 2008** Tutor am Histologischen Institut der Medizinischen Universität Wien

**2006 – 2007** Etablierung der 3D-Elektronmikroskopie im Zentrum für Anatomie und Zellbiologie, Medizinische Universität Wien

### ***Zertifizierungen***

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- Danksagung -

<b>2013</b>	MRT- Sachkundezertifikat, Circle Institut Berlin
<b>2012</b>	Herzschrittmacher-Sachkunde, Zertifizierung durch Deutsche Gesellschaft für Kardiologie
<b>2011</b>	ICD-Sachkunde und EPU, Zertifizierung durch Deutsche Gesellschaft für Kardiologie
<b>2010</b>	Zertifizierung in transoesophagaler Echokardiographie, Deutsche Gesellschaft für Kardiologie

### ***Wissenschaftliche Erfahrung***

---

<b>2009 – dato</b>	Initiieren, Durchführung und Koordination von laufenden wissenschaftlichen Projekten in der <b>Abteilung für Rhythmologie, Herzzentrum Leipzig</b>
<b>2006 – 2008</b>	Koautor des Projekts „ <i>Therapeutic angiogenesis by local overexpression of SDF-1</i> “ <b>Innere Medizin II, Abt.f. Angiologie, AKH Wien</b>
<b>2004 – 2008</b>	Autor des Projekts “ <i>Titel Morpho-functional studies of endothelial progenitor cells in their late stages of differentiation from umbilical cord blood stem cells</i> ” Zentrum für Anatomie und Zellbiologie, <b>Medizinischen Universität Wien</b>

### ***Publikationen***

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**Kosiuk J**, Gerhard H, Bollmann A: *Response to the letter "Worsened Diastology after Radiofrequency Catheter Ablation in AF Patients: More Touches More Stiff Left Atrium"* (International Journal of Cardiology, 2013)

**Kosiuk J**, Buchta P, Arya A, Rolf S, Piorkowski Ch, Gaspar T, Sommer Ph, Gerhard H, Bollmann A: *Prevalence and predictors of worsened left ventricular diastolic dysfunction after catheter ablation of atrial fibrillation* (International Journal of Cardiology, 2013)

**Kosiuk J**, Breithardt O, Bode K, Kornej J, Arya A, Gaspar T, Hindricks G, Bollmann A: *Left ventricular diastolic dysfunction and thromboembolic risk in atrial fibrillation* (International Journal of Cardiology, 2013)

- Danksagung -

**Kosiuk J**, Hindricks G, Bollmann A: *Letter regarding article, "symptoms and functional status of patients with atrial fibrillation: state of the art and future research opportunities" (Circulation, 2012)*

**Kosiuk J**, Van Belle Y, Bode K, Kornej J, Arya A, Rolf S, Husser D, Hindricks G, Bollmann A: *Left ventricular diastolic dysfunction in atrial fibrillation: predictors and relation with symptom severity. (Journal of Cardiovascular Electrophysiology 2012)*

Kornej J, Reinhardt C, **Kosiuk J**, Arya A, Hindricks G, Adams V, Husser D, Bollmann A: *Circulating heat shock protein 70 and anti-heat shock protein 70 antibodies in atrial fibrillation: Relation with atrial fibrillation type and response to catheter ablation. (PlusOne 2012)*

Kornej J, Reinhardt C, **Kosiuk J**, Arya A, Hindricks G, Adams V, Husser D, Bollmann A: *Response of high-sensitive C-reactive protein to catheter ablation of atrial fibrillation and its relation with rhythm outcome. (Journal of Translational Medicine, 2013)*

Kornej J, Hindricks G, **Kosiuk J**, Arya A, Sommer Ph, Husser D, Rolf S, Richter S, Piorkowski Ch, Gaspar T, Lip G.H. Bollmann A: *Renal Dysfunction, Stroke Risk Scores (CHADS2, CHA2DS2-VASc and R2CHADS2) and the Risk of Thromboembolic Events after Catheter Ablation of Atrial Fibrillation: The Leipzig Heart Center AF Ablation Registry. (Circulation: Arrhythmia and Electrophysiology, 2013)*

### ***Konferenzen (nur Erstautorschaften)***

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**Kosiuk J**, Dinov. B, Rolf S, Arya A, Piorkowski Ch, Gaspar T, Sommer Ph, Bollmann A, Hindricks G: *Calculating The Probability Of Presence Of Left Atrial Arrhythmogenic Substrate: Dr-Flash Score, (2013, Denver, USA) AHA Scientific Session*

**Kosiuk J**, Kotulas E, Nedios S, Rolf S, Arya A, Gaspar T, Sommer Ph, Hindricks G, Doering M, Richter S, Bollmann A: *Safety and efficacy of dabigatran compared with warfarin therapy in patients with atrial fibrillation undergoing cardiac rhythm device interventions. (2013, Amsterdam, Holland) ESC Congress,*

**Kosiuk J**, Bode K, Kornej J, Arya A, Gaspar T, Hindricks G, Bollmann A: *Early experience with dabigatran therapy in patients undergoing cardiac rhythm devices interventions: management and bleeding complications (2013, Athens, Greece) EHRA Congress,*

**Kosiuk J**, Nedios S, Darma A, Rolf S, Arya A, Piorkowski Ch, Gaspar T, Sommer Ph, Hindricks G, Bollmann A: *Predictors of long term outcome of single catheter ablation of atrial fibrillation in patients with ischemic and non-ischemic cardiomyopathies (2013, Dresden, Germany) DGK Congress,*

- Danksagung -

**Kosiuk J**, Nedios S, Darma A, Rolf S, Arya A, Piorkowski Ch, Gaspar T, Sommer Ph, Hindricks G, Bollmann A: *Treatment with novel oral anticoagulants in a real-world cohort of patients undergoing cardiac rhythm device implantations* (2013, Dresden, Germany) DGK Congress,

**Kosiuk J**, Nedios S, Darma A, Rolf S, Arya A, Piorkowski Ch, Gaspar T, Sommer Ph, Hindricks G, Bollmann A: *Predictors of mortality following the upgrade to cardiac resynchronisation therapy* (2013, Dresden, Germany) DGK Congress,

**Kosiuk J**, Kotulas E, Nedios S, Rolf S, Arya A, Gaspar T, Sommer Ph, Hindricks G, Doering M, Richter S, Bollmann A: *Safety and efficacy of rivaroxaban therapy in patients with atrial fibrillation undergoing cardiac rhythm device interventions*. (2013, Hong-Kong, China) APHRS Congress,

**Kosiuk J**, Nedios S, Darma A, Rolf S, Arya A, Piorkowski Ch, Gaspar T, Sommer Ph, Hindricks G, Bollmann A: *Predictors of long term outcome of single catheter ablation of atrial fibrillation in patients with ischemic and non-ischemic cardiomyopathies*. (2013, Hong-Kong, China) APHRS Congress,

**Kosiuk J**, Nedios S, Darma A, Rolf S, Arya A, Piorkowski Ch, Gaspar T, Sommer Ph, Hindricks G, Bollmann A: *Predictors of mortality following the upgrade to cardiac resynchronisation therapy* (2013, Hong-Kong, China) APHRS Congress,

**Kosiuk J**, Kornej J, Arya A, Piorkowski Ch, Gaspar T, Sommer Ph, Hindricks G, Lip GHY, Bollmann A: *Incidence, characteristic and risk factors of cerebral thromboembolic complications following high-frequency catheter ablation of atrial fibrillation: experience of 3360 procedures*. (2013 San Francisco, USA) ACC Scientific Session,

**Kosiuk J**, Kornej J, Bollman A, Arya A, Piorkowski Ch, Gaspar T, Sommer Ph, Lip GHY, Hindricks G: *Incidence, characteristic and risk factors of cerebral thromboembolic complications following high-frequency catheter ablation of atrial fibrillation: experience of 3360 procedures*. (2013, Mannheim, Germany),

**Kosiuk J**, Nedios S, Darma A, Rolf S, Arya A, Piorkowski Ch, Gaspar T, Sommer Ph, Hindricks G, Bollmann A: *Impact of Single Catheter Ablation of Atrial Fibrillation on Appropriate and Inappropriate Implantable Cardioverter Defibrillator Therapies in Patients with Cardiomyopathy* (2012 Los Angeles, USA) AHA Scientific Session,

**Kosiuk J**, Buchta P, Arya A, Piorkowski Ch, Gaspar T, Sommer Ph, Gerhard H, Bollmann A: *Prevalence and Predictors of Worsened Left Ventricular Diastolic Dysfunction After Catheter Ablation of Atrial Fibrillation* (2012 Los Angeles, USA) AHA Scientific Session,

**Kosiuk J**, Breithardt O, Bode K, Kornej J, Arya A, Gaspar T, Hindricks G, Bollmann A: *Left ventricular diastolic dysfunction and thromboembolic risk in atrial fibrillation* (2012, Boston, USA) HRS Congress,

- Danksagung -

**Kosiuk J**, Nedios S, Darma A, Rolf S, Arya A, Piorkowski Ch, Gaspar T, Sommer Ph, Hindricks G, Bollmann A: *Impact of Single Catheter Ablation of Atrial Fibrillation on Appropriate and Inappropriate Implantable Cardioverter Defibrillator Therapies in Patients with Cardiomyopathy* (2012, Hamburg, Germany) DGK Congress,

**Kosiuk J**, Buchta P, Arya A, Piorkowski Ch, Gaspar T, Sommer Ph, Gerhard H, Bollmann A: *Prevalence and Predictors of Worsened Left Ventricular Diastolic Dysfunction After Catheter Ablation of Atrial Fibrillation* (2012, Hamburg, Germany) DGK Congress,

**Kosiuk J**, Breithardt O, Bode K, Kornej J, Arya A, Gaspar T, Hindricks G, Bollmann A: *Left ventricular diastolic dysfunction and thromboembolic risk in atrial fibrillation* (2012, Mannheim, Germany) DGK Congress,

**Kosiuk J**, Bode K, Kornej J, Arya A, Gaspar T, Hindricks G, Bollmann A: *Left ventricular diastolic dysfunction in atrial fibrillation – predictors and relation with symptom severity and short-term outcome of catheter ablation* (2011, Paris, France) ESC Congress,

**Kosiuk J**, Bode K, Kornej J, Arya A, Gaspar T, Hindricks G, Bollmann A: *Echocardiographic predictors of early recurrence after catheter ablation of atrial fibrillation* (2011, Madrid, Spain) EHRA Congress,

**Kosiuk J**, Vetterlein M, Pavelka M, Neumueller J: *Endocytosis Studies in Endothelial Progenitor Cell*. (2006 Sapporo, Japan) *The 16th International Microscopy Congress*,

**Kosiuk J**, Vetterlein M, Pavelka M, Neumüller J: *Internalization of Wheat Germ Agglutinin in Endothelial Progenitor Cells in Conventional and Tomographic Electron Microscope Studies*. (2006 Chicago, USA) *Microscopy and Microanalysis Congress*,

**Kosiuk J**, Vetterlein M, Pavelka M, Neumüller J: *Weibel Palade bodies in close association with trans-Golgi network progenitor endothelial cells*. (2005 Davos, Switzerland) - Dreiländertagung Microscopy Conference,

### ***Preise und Auszeichnungen***

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Finalist, Hugo-von-Ziemssen Preis, Deutsche Gesellschaft für Kardiologie, 2012

Young Scientist Grant of Austrian Society of Electron Microscopy, 2006

### ***Andere Tätigkeiten***

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**2011 – dato**            Gründer und Koordinator von **Leipziger Selbsthilfegruppe für**

*- Danksagung -*

**Defi-Patienten**

<b>2012 – dato</b>	Reviewer für <b>European Heart Journal</b>
<b>2013 – dato</b>	Reviewer für <b>International Journal of Cardiology</b>
<b>2012 – dato</b>	Mietglied von European Heart Rhythm Association (EHRA)

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